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(54) Title: THE USE OF VALPROIC ACID ANALOG FOR THE TREATMENT AND PREVENTION OF MIGRAINE AND AFFECTIVE ILLNESS (57) Abstract This invention relates to a method for the treatment and prevention of migraine and affective illness by administering a therapeutically effective amount of the valproic acid analog 2-n-propyl-4-hexynoic acid. The compound 2-n-propyl-4-hexynoic acid is an effective anti-migraine and anti-affective illness drug with greatly reduced adverse effects including neurotoxicity and teratogenic potential compared to valproic acid. This invention thus provides an improved method for treating and preventing migraine and affective illness.		

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TITLE OF THE INVENTION**THE USE OF VALPROIC ACID ANALOG FOR THE TREATMENT
AND PREVENTION OF MIGRAINE AND AFFECTIVE ILLNESS**

This application claims priority to U.S. provisional application serial
number 60/090,281, filed June 22, 1998.

FIELD OF THE INVENTION

This invention relates to the valproic acid analog 2-n-propyl-4-hexynoic acid, and to its use for the treatment and prevention of migraine and affective illness. The valproic acid analog of the present invention is believed to be an effective anti-migraine and anti-affective illness drug with greatly reduced adverse effects including neurotoxicity and teratogenic potential compared to valproic acid. This invention thus provides an improved method for treating and preventing migraine and affective illness.

BACKGROUND OF THE INVENTION

Migraine is defined as a periodically occurring vascular headache characterized by pain in the head (usually unilateral), nausea and vomiting, photophobia, phonophobia, vertigo and general weakness. Migraine is the most common type of vascular headache and affects as many as 15% of the world's population. Of the different types of migraines, classical migraine and common migraine are the two most prevalent. The major difference between the two types of migraines is that classical migraines are preceded by the appearance of neurological symptoms before an attack whereas common migraines are not preceded by such symptoms. Migraine is caused by intermittent brain dysfunction. However, the precise pathophysiological mechanisms involved are not understood. The head pain is believed to involve blood vessel dilation and a reduction in the brain's pain-relieving chemicals.

Analgesics are often used to treat infrequent and mild migraines.

Analgesics reduce the pain of a migraine and in the case of aspirin also discourage clumping of blood platelets. However, for moderate to severe migraines, stronger medications such as ergotamine and valproic acid are necessary. Ergotamine tartrate is a vasoconstrictor which counteracts the painful dilation stage of the headache. When

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- taken during the early stages of an attack, ergotamine tartrate helps to relieve the classic and common migraine symptoms. Valproic acid has been shown to be effective in both the treatment and prevention of migraine, however, its mechanism of anti-migraine action is unclear. It is believed that valproic acid increases brain gamma-aminobutyric acid (GABA) levels and in doing so may activate the GABA receptor and suppresses migraine-related events.

A relationship has been reported between migraine, affective illness and epilepsy. Although the three disorders are distinct, they all are paroxysmal dysregulations of the nervous system that partially overlap in their pharmacology. Some drugs, such as valproic acid, are effective in treating all three syndromes, suggesting the presence of shared underlying pathophysiology, while other drugs are effective for treating one syndrome. For example, beta blockers which are effective against migraine are not useful for treating the other two syndromes and may even exasperate depression.

The kindling model for complex-partial seizures is based on the progressive development of seizures combined with electroencephalographic (EEG) paroxysmal patterns induced by repeated initially subconvulsive electrical stimulation of limbic structures, e.g. the basolateral nucleus of the amygdala. Once established, the phenomenon persists for months. Since the amygdala kindled seizures in animals share numerous characteristics with complex-partial seizures in humans, it is presently the best animal model of complex partial seizures (Goddard et al. 1969; Löscher and Schmidt 1988; Löscher 1993). One major advantage of using the amygdala kindling model is that both behavioral and EEG parameters of the partial and generalized seizures can be measured. Furthermore, the amygdala kindling model is reported to be appropriate for studying diseases such as migraine, affective illness and epilepsy which increase in severity overtime and in a manner which is related to the number of symptomatic episodes.

Previously, the valproic acid analog 2-n-propyl-4-hexynoic acid was shown to be an improved antiepileptic compared to valproic acid by the subcutaneous pentetrazole convulsion test (PTZ test). Experimental findings from various studies in

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- which both the PTZ test and the amygdala kindling test were employed indicate that drugs that are effective against the PTZ induced seizures are not necessarily effective against amygdala kindled seizures and vice versa (Loscher, W., and Honack, Dagmar., Eur.J. Pharmacol. (1993), 232:147-158; Johnson, D. et al., Epilepsy Res. (1991), 8:64-70). Therefore, not all anticonvulsant are effective against amygdala kindled seizures. In other words, drugs that are antiepileptics are not necessarily effective in the treatment of migraine or affective illness.

Recent publications suggest that the amygdala kindling model is appropriate for studying shared mechanisms underlying the increase in severity over time of symptomatic episodes in epilepsy, migraine and affective illness (R. Post and S. Silberstein, Neurology (1994), 44: S37-S47; R. Post and S. Weiss, Molecular Neurobiology (1996), 13:33-60). In amygdala kindling, intermittent electrical stimulation of the amygdala of the brain is first without effect, but eventually following repeated stimulation, results in increasing biochemical and physiological responses cumulating in a full-blown convulsion. Following continued triggering of seizures, seizures begin to emerge spontaneously. This progression of symptom severity involves a long-lasting change in the property of the neuron. Experimental findings indicate that kindling induced in animals shares many features with human affective illness, migraine and epilepsy, such as progression from triggered to spontaneous, changes in behavior patterns during the seizure and responsiveness to certain anti-seizure drugs. Therefore, amygdala kindling may serve as a model to study the possible underlying mechanisms for the memory-like processes that may be involved in migraine, affective illness and epilepsy.

U.S. Patent 4,942,182 reports the stage dependent sensitivity to drug treatment of seizures induced by amygdala kindling. In this model, carbamazepine suppresses complete amygdala-kindled seizures in rats, but is ineffective in preventing their development. Diazepam however, which is effective in inhibiting the earlier stages of seizure development is not effective during the late stages when seizures occur spontaneously. Phenytoin, another anticonvulsant drug has activity opposite that of diazepam being an effective block of spontaneous seizures, but not seizures elicited

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- during the early stages of kindling.

The amygdala kindling model is also an important model to evaluate potentially useful drugs because it can provide information different from that of other seizure models. For example, whereas carbamazepine is an effective anti-convulsant in several seizure models including the amygdala kindling model, it is less effective on
5 seizures induced by pentylenetetrazole and high dose picrotoxin.

Valproic acid is an effective drug for the treatment and prevention of epilepsy, migraine and affective illness. However, it has a short duration of action, and suffers from serious side effects such as sedation, potentially fatal hepatotoxicity and
10 teratogenicity. There has been a considerable effort to discover analogs of valproic acid that are equally effective, but have a longer duration of activity and a greater margin of safety. One study has demonstrated that the valproic acid analog 2-n-propyl-4-hexynoic acid is an effective antiepileptic with a longer duration of activity and greatly
15 reduced sedative and teratogenic effects compared to valproic acid (Nau et al, U.S. Application 08/344,810, which is hereby incorporated in its entirety by reference). The compound 2-n-propyl-4-hexynoic acid is therefore an improved antiepileptic. However, since the compound was only examined in the subcutaneous pentetrazole convulsion test (PTZ test) which is designed to evaluate the effectiveness of drugs
20 against epilepsy, the effectiveness of the compound for the treatment of migraine or affective illness is not known.

SUMMARY OF THE INVENTION

25 This invention relates to the compound 2-n-propyl-4-hexynoic acid, pharmaceutical compositions containing this compound, and their use to treat and/or prevent migraine and affective illness. The compound for use in this invention is believed to be effective in the treatment and prevention of migraine and affective
30 illness, and exhibits greatly reduced adverse effects and longer duration of activity, when compared to valproic acid.

One object of this invention is to provide a method for treating and/or preventing migraine and affective illness (including unipolar, bipolar illness and acute
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- mania) due to a variety of causes, by administering to an individual in need of such treatment a therapeutically or prophylactically effective amount of 2-n-propyl-4-hexynoic acid.

Another object of this invention is to provide pharmaceutical compositions for the treatment and/or prevention of migraine and affective illness that has longer duration of activity, exhibits lower adverse effects, and avoids teratogenic toxicity compared to valproic acid.

DETAILED DESCRIPTION OF THE INVENTION

This invention relates to the use of the valproic acid analog 2-n-propyl-4-hexynoic acid as a treatment and prevention for migraine and affective illness.

This invention provides a method of treating and preventing migraine or affective illness in individuals by administering 2-n-propyl-4-hexynoic acid. The synthesis and desirable metabolic properties of 2-n-propyl-4-hexynoic acid are fully disclosed in U.S. Patent 5,786,380 (Examples 7-8 and 10-11) which is incorporated herein by reference in its entirety. Mammals, and in particular humans, who would benefit from this method of treatment include those exhibiting, or at risk for exhibiting, any type of recurring headaches, especially vascular headaches and those which are moderate or severe. Individuals suffering from migraine are expected to benefit from administration of 2-n-propyl-4-hexynoic acid. The method of the invention comprises administering to an individual a therapeutically effective amount of 2-propyl-4-hexynoic acid which is sufficient to reduce or prevent migraine or affective illness.

In contrast to valproic acid, the compound for use with this invention exhibits greatly reduced adverse effects and teratogenicity, and has a longer duration of activity.

The data presented here show that like valproic acid, 2-n-propyl-4-hexynoic acid is expected to be effective against amygdala kindled seizures. Furthermore, it exhibits adverse effects only at the highest dose tested and those effects are much milder compared to that of valproic acid. Therefore, 2-propyl-4-hexynoic acid provides an improved method for the treatment and prevention of migraine and

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° affective illness.

The compound 2-propyl-4-hexynoic acid is effective for the treatment of acute mania with bipolar disorder. Typical manic symptoms include pressure of speech, motor hyperactivity, reduced need for sleep, flight of ideas, grandiosity, poor judgement, aggressiveness, and possible hostility.

The compound 2-propyl-4-hexynoic acid is also effective for the prevention and treatment of migraine headaches.

It will be apparent to those skilled in the art that the compound 2-propyl-4-hexynoic acid for use with this invention may exist in enantiomeric forms. Pure enantiomers may be resolved from the racemate by methods well known in the art. Alternatively, enantiomeric forms may be prepared by chiral synthesis. Individual R and S enantiomers, racemates and non-racemic mixtures of enantiomers of 2-n-propyl-4-hexynoic acid are all within the scope of this invention. When the individual enantiomers are used, the S enantiomer of 2-n-propyl-4-hexynoic acid is preferred if one needs to take advantage of the apparent higher pharmacokinetic profile of the S enantiomer. However, if maximal avoidance of teratogenic side effects is required, then the R enantiomer is the preferred form.

The dose of the compound used in the treatment of such disease will vary in the usual way with the seriousness of the disorder, the weight and metabolic health of the sufferer. The preferred initial dose for the general patient population will be determined by routine dose-ranging studies, as are conducted for example during clinical trials. Therapeutically effective doses for individual patients may be determined by titrating the amount of drug given to the individual to arrive at the desired therapeutic or prophylactic effect while minimizing side effects. Dosages may be similar to those used with valproic acid, however, they may be adjusted appropriately, based on the potencies and kinetic parameters disclosed herein or as determined by routine methods. A preferred initial dose for this compound, may be estimated to be between about 1 and 60 mg/kg/day, more preferably between 10-20 mg/kg/day. The preferred plasma concentration for patients taking 2-n-propyl-4-hexynoic acid is between 50-100 ug/ml.

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- Administration of the compounds of this invention may be by any method used for administering therapeutics, such as for example oral, parenteral, intravenous, intramuscular, subcutaneous, or rectal administration.

This invention also provides pharmaceutical compositions for the treatment of migraine. In addition to comprising the compound 2-n-propyl-hexynoic acid or a salt or pro-drug thereof, the pharmaceutical composition may also comprise additives such as preservatives, excipients, fillers, wetting agents, binders, disintegrants, buffers, and/or carriers. Suitable additives may be for example magnesium and calcium carbonates, carboxymethylcellulose, starches, sugars, gums, magnesium or calcium stearate, coloring or flavoring agents, and the like. There exists a wide variety of pharmaceutically acceptable additives for pharmaceutical dosage forms, and selection of appropriate additives is a routine matter for those skilled in art of pharmaceutical formulation.

The compositions may be in the form of tablets, capsules, powders, granules, lozenges, suppositories, reconstitutable powders, or liquid preparations such as oral or sterile parenteral solutions or suspensions.

In order to obtain consistency of administration it is preferred that a composition of the invention is in the form of a unit dose. Unit dose forms for oral administration may be tablets, capsules, and the like, and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrrolidone; and carriers or fillers, for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine. Additives may include disintegrants, for example starch, polyvinylpyrrolidone, sodium starch glycolate or microcrystalline cellulose; preservatives, and pharmaceutically acceptable wetting agents such as sodium lauryl sulphate.

In addition to unit dose forms, multi-dosage forms are also contemplated to be within the scope of the invention. Delayed-release compositions, for example those prepared by employing slow-release coatings, micro-encapsulation, and/or slowly-dissolving polymer carriers, will also be apparent to those skilled in the art, and are contemplated to be within the scope of the invention.

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o The solid oral compositions may be prepared by conventional methods of blending, filling, tableting or the like. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. Such operations are conventional in the art. The tablets may be coated according to methods well known in normal pharmaceutical practice, for example with an enteric coating.

Oral liquid preparations may be in the form of, for example, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminum stearate gel, and hydrogenated edible fats; emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil or fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid; and if desired conventional flavoring or coloring agents.

For parenteral administration, fluid unit dosage forms are prepared utilizing the compound and a sterile vehicle, and, depending on the concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions the compound can be dissolved in water or saline for injection and filter sterilized before filling into a suitable vial or ampoule and sealing. Advantageously, additives such as a local anaesthetic, preservative and buffering agent can be dissolved in the vehicle. Suitable buffering agents are, for example, phosphate and citrate salts. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilization cannot be accomplished by filtration. The compound can be sterilized by conventional means, for example by exposure to radiation or ethylene oxide, before being suspended in the sterile vehicle. Advantageously, a surfactant or wetting agent is

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- included in the composition to facilitate uniform distribution of the compound.

The present invention will now be described by way of examples, which are meant to illustrate, but not limit, the scope of the invention.

EXAMPLE 1

5 In Example 1, the anti-migraine and anti-affective illness profiles of 2-n-propyl-4-hexynoic acid and valproic acid are compared in the amygdala kindling model.

Materials and Methods

10 Animals

Female Wistar rats (Harlan-Winkelmann, Borcheln, Germany) were obtained at an age of 11-12 weeks (body weight 180-200 g). Female rats were employed because they are known to eliminate drugs less rapidly than do males, which was thought to be an advantage for drug potency studies. Rats were kept separately in plastic cages at controlled temperature (23°C) and humidity (about 50 %) with a 12-h light cycle beginning at 7 a.m. They received standard diet (Altromin; Lage, F.R.G.), tap water and libitum. All drug injections were done in the afternoon at an ambient temperature of 23-25°C. The regular protocol started by taking the rats out of their individual cage, weighing them and joining them together on a table with six open plastic cages for better behavioral observations. Therefore animals were able to move from one cage to another and either to have social contact or to avoid it. After a short adaptation time of approximately 15 minutes, rectal body temperatures were recorded followed by drug or vehicle application.

25 Amygdala-kindling in rats

For implantation of stimulation and recording electrodes, rats were anesthetized with chloral hydrate (360 mg/kg i.p.) and received stereotaxic implantation (according to the surgery methods described in the atlas of Paxinos and Watson [1986]) of one bipolar electrode in the right basolateral amygdala. Coordinates for electrode implantation were AP-2.2 mm, L-4.8 mm, V-8.5 mm. All coordinates were measured from bregma. Skull screws served as the indifferent reference electrode. The electrode

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assembly was attached to the skull by dental acrylic cement. After a postoperative period of 2 weeks, constant current stimulations (500 μ A, 1 ms. monophasic square-wave pulses, 50/s for 1 s) were delivered to the amygdala at intervals of 1/day until ten stage 5 seizures were elicited. The electrical susceptibility of the stimulated region (threshold for induction of afterdischarges) was recorded on the first day of the experiment (initial afterdischarge threshold) as well as after kindling acquisition (with an interval of at least 4 days after the tenth stage 5 seizure) using an ascending staircase procedure. The initial current intensity was 10 μ A, and the current intensity was increased in steps of about 20% of the previous current at intervals of 1 min until an afterdischarge of at least 3 s duration was elicited. Since almost all fully kindled animals exhibited generalized seizures (stage 4-5) at the afterdischarge threshold current, it was not necessary to determine the threshold for generalized seizures separately. In addition to afterdischarge threshold, the following parameters of kindled seizures were measured in fully-kindled rats after stimulation with the afterdischarge threshold current: seizure severity was classified according to Racine (1972): 1-immobility, eye closure, twitching of vibrissae, sniffing, facial clonus; 2-head nodding associated with more severe facial clonus; 3-clonus of one forelimb; 4-rearing, often accompanied by bilateral forelimb clonus; 5-rearing with loss of balance and falling accompanied by generalized clonic seizures. Seizure duration 1 (SD 1) was the duration of limbic (stage 1-2) and/or motor seizures (stage 3-5). Seizure duration 2 (SD 2) included the time of limbic and/or motor seizures plus the adjacent time of immobility. Afterdischarge duration 1 (ADD1) was the time of spikes in the EEG recorded from the site of stimulation with a frequency of at least 1/s. Afterdischarge duration 2 (ADD 2) was the total time of spikes occurring in the EEG including those, which followed the ADD 1 with lower frequency and amplitude.

The anti-seizure effects of 2-propyl-4-hexynoic acid and valproate in fully kindled rats were determined in a group of 8-9 rats (no. 784, 785, 787, 788, 789, 790 [had to be taken out of the trial, because of loss of electrodes], 791, 792, 793) with reproducible stage 5 seizures.

Drugs were injected 15 min prior to stimulation intraperitoneally.

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- Control experiments were always performed 2-3 days before each drug experiment. For control determinations, rats received i.p. injections of vehicle (saline) with the pretreatment time of the respective drug experiment. For all drug experiments, at least 4 days were interposed between 2 drug injections in order to avoid alterations in drug potency due to cumulation or tolerance.

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The significance of differences between pre-drug control recordings and recordings after drug injection was calculated by the Wilcoxon signed rank test for paired replicates (SigmaStat for Windows, version 1.0).

10 Tests used for quantification of adverse effects

In addition to recordings of anticonvulsant parameters, kindled rats were observed for adverse effects in order to estimate a therapeutic index. Tests included open field observations, rotarod test and body temperature. Tests were always performed in the same manner in control and drug experiments at two different times, just before application of drug or vehicle and 13 minutes after application.

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The rotarod test was carried out with a rod of 6 cm diameter and rotation speed of 8 r.p.m. Neurological deficit was indicated by inability of the animals to maintain their equilibrium for at least 1 min on the rotating rod. Rats had to be trained prior to drug experiments to maintain their balance on the rod. After drug or vehicle treatment, rats which were not able to maintain their equilibrium on the rod for 1 minute were put again on the rod twice. Only animals which were not able to remain on the rod for three subsequent 1 minute attempts were considered to exhibit neurological deficit.

25

In addition to these quantitative estimations of neurological deficit, behavioral alterations observed after administration of 2-propyl-4-hexynoic acid and valproate noted in the cage and by placing the animals in an open field of 90-100 cm diameter. Muscle tone was estimated by palpation of the abdomen. The extent of deficits in behavior after administration of the compounds was determined by a rating system (Löscher et al. 1987). In short, animals were taken out of the cage, placed in an open field, observed for about 1 minute and rated separately for ataxia, abducted hindlimbs, reduced righting, flat body posture, circling, Straub tail, piloerection,

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- hypolocomotion and hyperlocomotion (abdominal muscle tone was evaluated by palpation at the end of the period of observation). All other parameters except ataxia were scored from 0 to 3: 0-absent; 1-equivocal; 2-present; 3- intense. For ataxia (06): 1-slight ataxia in hind-legs (tottering of the hind quarters); 2-more pronounced ataxia with dragging of hind legs; 3-further increase of ataxia and more pronounced dragging of hind legs; 4-marked ataxia, animals lose balance during forward locomotion; 5- very marked ataxia with frequent loss of balance during forward locomotion; 6-permanent loss of righting reflexes, but animal still attempts to move forward. Rectal body temperature was measured by an electronic thermometer. Body weight of the animals was recorded once daily before drug injection. Significance of differences in behavior between pre-drug and post-drug data determined in the same group of animals was calculated by the Wilcoxon signed rank test for paired replicates and for body temperature by Student's paired t-test (SigmaStat for Windows, version 1.0). Differences in body temperature were always compared only within the experimental day with the pre-drug time as control to one post-drug time.

Test drugs

The compound 2-propyl-4-hexynoic acid (MW 154) was melted in a water bath at 40°C for approximately 30 min and then transferred to an equimolar volume of 1 molar NaOH of similar temperature. After formation of the sodium salt it was dissolved in saline to a volume of 2.5 ml/kg in rats, and 10 ml/kg in mice, respectively. Valproate (dissolved in water as sodium salt) was a gift of Desitin Arzneimittel GmbH, Hamburg, Germany. The stock solution had a concentration of 100 mg/ml (calculated as free acid) and was therefore dissolved in saline to receive equivalent injection volumes as for 2-propyl-4-hexynoic acid. All drug doses given in this study refer to the free (acid) forms.

Since there were differences in potencies between both compounds, plasma was obtained from rats immediately after treatment and kindling stimulation during one dose experiment.

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Results

Amygdala-kindling and adverse effects in rats

Both compounds were tested at the following doses in fully amygdala-kindled rats: 50, 75, 100, and 200 mg/kg i.p. after 15 min pretreatment time. For valproate significant effects against amygdala-kindled seizures (Tables 1-4) were observed at all doses tested. The lower doses of 50 and 75 mg/kg i.p. increased the threshold significantly by means of 109% and 77%, respectively. At 100 mg/kg i.p. significant effects on all kindling parameters were observed. The average electrical threshold for induction of after discharges was increased by 319% (Table 3). If all rats would have been stimulated at 20% above their individual threshold only (which several groups use as kindling stimulus), all rats would have been totally protected against seizures. Seizure severity was significantly decreased from 5.0 to 3.0. Seizure duration was reduced from an average of 81 to 18 s and total afterdischarge duration (ADD 2) was reduced from 95 to 20 s. No alterations in behavior and body-temperature were observed. Rotarod test was performed without failure.

With 200 mg/kg valproate the response to the kindling parameters increased with threshold increase of 970%, decrease of seizure severity from 4.9 to 1.6, reduction of seizure duration from 73 to 9 s and reduction of afterdischarge duration from 106 to 9 s (Table 4). As expected from earlier experiments this dosage was combined with several adverse effects like obvious ataxia (average score 2.8 after 13 min pretreatment time), hypolocomotion (1.0), muscle relaxation (2.0) and wet dog shakes. The rotarod-test on the other hand was performed without failure. Body-temperature increased up to 39.2°C.

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TABLE I
Anti-Seizure Activity And Adverse Effects of Valproate At 50 mg/kg

animal	784	785	787	788	789	790	791	792	793	X	S.E.M.	stat. sign
KINDLING												
afterdisch.thresh.	30	20	30	15	36	20	42	42	25	28.89	3.26	
(ADT; μ A)	50	110	36	75	42	75	60	60	36	60.44	7.93	0.002
seizure severity	5	5	5	5	5	5	5	5	5	5.00	0.00	
(SS; score)	4	5	1	4	5	5	5	5	5	4.33	0.44	n.s
seizure duration 1	60	71	30	80	65	71	52	84	88	66.78	5.98	
(SD1; sec)	58	64	6	95	88	73	83	95	88	72.22	9.36	n.s
seizure duration 2	279	244	122	283	250	242	123	245	256	227.11	20.37	
(SD2; sec)	320	214	6	314	268	280	198	245	240	231.67	31.37	n.s
afterdisch.dur.1	161	68	30	80	65	71	52	94	88	78.78	12.10	
(ADD1; sec)	67	83	6	107	88	73	83	95	88	76.67	9.64	n.s
afterdisch.dur.2	161	78	30	80	65	71	52	94	88	79.89	12.03	
(ADD2; sec)	67	83	6	107	88	73	83	95	88	76.67	9.64	n.s
BODY TEMP. (°C)												
ante appl.	38.8	39.0	38.5	39.1	38.8	38.7	38.9	39.0	38.9	38.86	0.06	control
13' post appl.	38.7	38.6	38.7	38.8.0	38.7	38.8	39.0	38.7	38.7	38.71	0.05	n.s
ante appl.	38.8	39.1	38.5	39.1	39.1	38.6	38.4	38.7	38.8	38.79	0.09	control
13' post appl.	38.7	39.0	38.7	39.0	38.8	38.7	39.0	39.0	38.5	38.82	0.06	n.s

Wilcoxon

t-test

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[illegible]

TABLE 2
Anti-Seizure Activity And Adverse Effects of Valproate At 75 mg/kg

animal	784	785	787	788	789	791	792	793	X	S.E.M.	Signifikanz Wilcoxon
KINDLING											
afterdisch.thresh.	20	30	25	15	50	50	110	30	41.25	10.80	
(ADT; μ A)	50	75	60	25	110	60	130	75	73.13	11.80	0.0039
seizure severity	5	5	5	5	5	5	5	5	5.00	0.00	
(SS; score)	4	5	4	5	2	3	5	5	4.13	0.40	n.s
seizure duration1	47	68	84	65	81	41	70	92	68.50	6.24	
(SD1; sec)	20	65	65	95	9	18	60	100	54.00	12.36	n.s
seizure duration2	267	218	202	327	348	120	266	100	249.75	25.46	
(SD2; sec)	30	445	300	343	9	18	392	465	250.75	70.19	n.s
afterdisch.dur.1	94	77	125	64	86	41	82	92	82.63	8.59	
(ADD1; sec)	20	87	95	104	9	18	102	103	67.25	15.26	n.s
afterdisch.dur.2	94	77	125	64	86	41	82	92	82.63	8.59	
(ADD2; sec)	20	87	95	104	9	18	102	103	67.25	15.26	n.s
BODY TEMP. (°C)											
ante appl.	38.5	38.2	38.8	37.8	37.8	38.9	38.2	38.5	38.34	0.15	control
13' post appl.	38.7	38.8	38.9	38.9	38.9	39.1	38.4	39.0	38.84	0.08	0.0103
ante appl.	38.6	38.2	38.1	38.1	38.8	38.8	38.4	38.8	38.48	0.11	control
13' post appl.	38.7	39.0	38.6	38.4	37.4	39.2	38.4	38.7	38.55	0.19	n.s

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[illegible]

TABLE 3
Anti-Seizure Activity And Adverse Effects of Valproate At 100 mg/kg

animal	784	785	787	788	789	790	791	792	793	X	S.E.M.	stat. sign
KINDLING												<i>Wilcoxon</i>
afterdisch.thresh.												
(ADT; μ A)	30	10	20	15	36	10	90	90	25	36.22	10.57	
seizure severity	75	130	60	200	130	160	240	240	130	151.67	21.63	0.0020
(SS; score)	5	5	5	5	5	5	5	5	5	5.00	0.00	
seizure duration1	2	3	3	3	2	4	2	5	3	3.00	0.33	0.0039
(SD1; sec)	60	55	70	65	92	91	138	77	85	81.44	8.33	
seizure duration2	22	5	5	13	6	5	6	84	18	18.22	8.49	0.0039
(SD2; sec)	260	205	218	241	153	216	238	280	303	234.89	14.72	
afterdisch.dur.1	22	5	5	13	6	5	6	310	18	43.44	33.40	0.0039
(ADD1; sec)	60	5	70	65	92	91	138	77	85	81.44	8.33	
afterdisch.dur.2	22	5	5	13	6	5	6	100	18	20.00	10.22	0.0039
(ADD2; sec)	145	55	107	65	92	91	138	77	85	95.00	10.17	
BODY TEMP. ($^{\circ}$ C)	22	5	5	13	6	5	6	100	18	20.00	10.22	0.0039
ante appl.	38.4	38.9	38.3	37.6	38.4	37.6	38.0	38.6	39.0	38.31	0.17	control
13' post appl.	38.0	39.0	38.5	38.7	38.5	38.6	37.9	38.3	38.8	38.48	0.12	n.s.
ante appl.	38.4	38.5	38.0	38.5	38.4	37.8	38.5	38.2	38.9	38.36	0.11	control
13' post appl.	38.9	38.9	38.9	39.0	39.0	39.1	39.2	38.9	38.8	38.97	0.04	0.0013

TABLE 4

Anti-Seizure Activity And Adverse Effects of Valproate At 200 mg/kg

animal	784	785	787	788	789	791	792	793	X	S.F.M.	stat. sign.
KINDLING											<i>Wilcoxon</i>
afterdisch. thresh.	36	25	25	20	25	60	130	50	46.38	12.93	
(ADT; μ A)	130	840	590	840	200	840	330	200	496.25	111.85	0.0039
seizure severity	5	5	5	5	5	4	5	5	4.88	0.13	
(SS; score)	2	3	3	1	1	1	1	1	1.63	0.32	0.0039
seizure duration 1	46	60	90	75	98	50	68	98	73.13	7.31	
(SD1; sec)	8	18	9	8	6	5	5	11	8.75	1.51	0.0039
seizure duration 2	321	229	338	241	361	232	298	295	289.38	17.87	
(SD2; sec)	8	18	9	8	6	5	5	11	8.75	1.51	0.0039
afterdisch. dur. 1	133	78	172	75	98	50	105	100	101.38	13.29	
(ADD1; sec)	8	18	9	8	6	5	5	11	8.75	1.51	0.0039
afterdisch. dur. 2	133	78	172	111	98	50	105	100	105.88	12.77	
(ADD2; sec)	8	18	9	8	6	5	5	11	8.75	1.51	0.0039
BODY TEMP.											<i>t-Test</i>
(°C)											
ante appl.	37.9	38.0	37.7	38.4	38.3	38.2	38.1	37.9	38.06	0.08	control
13' post appl.	37.9	39.0	38.7	38.2	38.4	38.7	38.2	38.5	38.45	0.12	0.048
ante appl.	38.2	38.5	39.1	38.6	38.8	38.9	38.6	38.9	38.70	0.10	control
13' post appl.	39.1	39.7	39.4	38.6	39.1	39.3	38.9	39.3	39.18	0.12	0.01

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BEHAVIOR	(score)											2.75	0.25	0.0039
		3	2	3	2	3	2	3	2	3	2			
ataxia	13'													
(1-6)														
abduct. hindlimb	13'													
(1-3)														
red. righting	13'													
(1-3)														
(flat body posture)	13'													
(1-3)														
circling	13'													
(1-3)														
Straub tail	13'													
(1-3)														
piloerection	13'													
(1-3)														
hypolocomotion	13'	1	1	1	1	1	1	1	1	1	1	1.00	0.00	0.0039
(1-3)														
hyperlocomotion	13'													
(1-3)														
muscle relaxation	13'	2	2	2	2	2	2	2	2	2	2	2.00	0.00	0.0039
(1-3)														
rotarod-test	13'	+	+	+	+	+	+	+	+	+	+	0%		
day of exper														

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In comparison, 2-propyl-4-hexynoic acid exerted no significant effects at a dose of 50 mg/kg i.p. (Table 5). At 75 mg/kg, the threshold was increased up to 109%, and the seizure severity was decreased significantly from an average score of 5.0 to 2.3 (Table 6). Seizure duration was reduced from 66 to 16 s and afterdischarge duration was reduced from 86 to 16 s. The dosage of 100 mg/kg (Table 7) increased the threshold by means of 160%. The decrease of seizure severity from 5.0 to 3.6 was less than with lower dose. The same accounts for seizure duration, which was reduced from 83 to 47 s. Maximal effects against amygdala-kindled seizures were achieved with the highest dose tested. 200 mg/kg (Table 8) increased the threshold by means of 209%, seizure severity was significantly decreased from 4.6 to 1.8. Seizure duration was reduced from an average of 62 to 19 s, and total afterdischarge duration (ADD 2) was reduced from 77 to 24 s.

Adverse effects were only observed at the highest dose of 200 mg/kg and were milder than with valproate with mild ataxia (mean score 1.5), hypolocomotion (1.4) and muscle relaxation (1.4). Body-temperatures maintained within the physiological range and rotarod-test was performed successfully by all individuals.

TABLE 5

Anti-Seizure Activity And Adverse Effects of 2-propyl-4-hexynoic acid at 50 mg/kg

animal	784	785	787	788	789	791	792	793	X	S.E.M.	stat. sign.
KINDLING											
afterdisch.thresh.	42	20	25	15	36	20	60	42	25	31.67	4.82
(ADT; μ A)	42	36	30	20	42	30	50	50	36	37.33	3.28
seizure severity	5	4	5	5	5	5	5	5	5	4.89	0.11
(SS; score)	5	5	4	5	5	5	5	5	5	4.89	0.11
seizure duration1	67	59	83	93	92	65	172	72	90	88.11	11.30
(SD1; sec)	74	79	81	88	98	77	64	52	93	78.44	4.75
seizure duration2	289	121	282	335	253	174	260	293	280	254.11	22.01
(SD2; sec)	254	200	198	288	270	224	217	164	294	234.33	14.88
afterdisch.dur.1	68	59	83	11	92	65	172	99	90	93.22	11.35
(ADD1; sec)	161	79	114	88	97	91	64	52	92	93.11	10.43
afterdisch.dur.2	68	59	83	11	92	65	172	99	90	93.22	11.35
(ADD2; sec)	161	79	114	88	97	91	64	52	92	93.11	10.43
BODY TEMP. (°C)											
ante appl.	38.0	38.5	38.1	37.7	38.6	38.6	38.4	38.3	38.8	38.33	0.12
13' post appl.	38.5	38.4	38.3	38.4	38.7	39.0	38.5	38.2	38.8	38.53	0.08
ante appl.	37.4	38.5	38.3	38.7	38.2	38.6	38.6	38.9	38.8	38.44	0.15
13' post appl.	37.6	38.9	38.3	38.3	38.6	38.5	38.7	38.6	38.8	38.48	0.13

Wilcoxon

t-Test

control

n.s.

n.s.

n.s.

n.s.

n.s.

n.s.

n.s.

n.s.

TABLE 6

Anti-Seizure Activity And Adverse Effects Of 2-propyl-4-hexynoic acid at 75^{mg}/kg

animal	784	785	787	788	789	791	792	793	\bar{X}	S.E.M.	stat. sign.
KINDLING											
afterdisch.thresh.	36	10	36	10	30	90	90	36	42.25	11.11	
(ADT; μ A)	18	90	90	90	110	90	160	60	88.50	14.25	0.0157
seizure severity	5	5	5	5	5	5	5	5	5.00	0.00	
(SS; score)	1	2	3	3	1	3	4	1	2.25	0.41	0.0039
seizure duration1	48	64	80	65	92	42	54	85	66.25	6.38	
(SD1; sec)	18	6	7	5	8	35	26	25	16.25	4.03	0.0039
seizure duration2	348	240	210	180	120	230	398	260	248.25	31.48	
(SD2; sec)	18	6	7	5	8	35	26	25	16.25	4.03	0.0039
afterdisch.dur.1	108	79	107	65	106	42	93	85	85.63	8.24	
(ADD1; sec)	18	6	7	5	8	35	26	25	16.25	4.03	0.0039
afterdisch.dur.2	108	79	107	65	106	42	93	85	85.63	8.24	
(ADD2; sec)	18	6	7	5	8	35	26	25	16.25	4.03	0.0039
BODY TEMP.											
	(°C)										
ante appl.	38.6	38.9	39.0	38.7	38.9	39.2	39.0	39.2	38.94	0.08	control
13' post appl.	39.2	39.0	38.8	38.5	39.0	38.7	38.2	38.7	38.76	0.11	n.s.
ante appl.	37.8	38.2	38.0	37.9	38.5	38.3	37.9	38.4	38.13	0.09	control
13' post appl.	38.3	38.6	38.8	38.6	38.5	38.6	38.2	38.3	38.49	0.07	0.0133

Wilcoxon

t-Test

control

n.s.

control

0.0133

TABLE 7
Anti-Seizure Activity And Adverse Effects of 2-propyl-4-hexynoic acid at 100 mg/kg

animal	784	785	787	788	789	791	792	793	X	S.E.M.	stat. sign.
KINDLING											Wilcoxon
afterdisch.thresh.	42	36	20	25	30	75	130	30	48.50	13.09	
(ADT, μ A)	60	130	75	200	110	200	160	75	126.25	19.79	0.0039
seizure severity	5	5	5	5	5	5	5	5	5.00	0.00	
(SS; score)	5	4	2	3	2	3	5	5	3.63	0.46	0.0313
seizure duration1	60	90	80	79	114	67	84	90	83.00	5.78	
(SD1; sec)	57	5	5	5	10	130	75	85	46.50	16.84	0.0274
seizure duration2	310	280	200	318	261	168	280	253	258.75	18.31	
(SD2; sec)	180	5	5	5	10	130	275	235	105.63	40.33	0.0039
afterdisch.dur.1	71	90	80	93	114	67	84	89	86.00	5.15	
(ADD1; sec)	145	5	5	5	10	130	107	95	62.75	21.99	n.s.
afterdisch.dur.2	78	90	80	93	14	67	84	89	86.88	4.85	
(ADD2; sec)	145	5	5	5	10	130	107	95	62.75	21.99	n.s.
BODY TEMP.											t-Test
(°C)											
ante appl.	38.5	38.4	38.2	38.6	39.0	38.5	38.2	38.2	38.45	0.10	control
13' post appl.	38.4	38.6	38.1	38.8	38.8	38.6	38.4	38.5	38.52	0.0	n.s.
day of exper.											
ante appl.	38.4	38.7	38.7	38.9	39.1	38.4	38.6	38.9	38.71	0.09	control
13' post appl.	38.3	38.7	38.4	38.1	38.1	38.5	38.0	38.4	38.31	0.08	0.0236

[illegible]

TABLE 8

Anti-Seizure Activity And Adverse Effects of 2-propyl-4-hexynoic acid at 200 mg/kg

animal	784	785	787	788	789	791	792	793	X	S.E.M.	stat. sign.
KINDLING											<i>Wilcoxon</i>
afterdisch.thresh.	42	20	30	15	30	200	90	36	57.88	21.87	
(ADT; μ A)	110	160	160	200	110	330	160	200	178.75	24.74	0.0039
seizure severity	5	5	5	5	4	3	5	5	4.63	0.26	
(SS; score)	1	1	5	1	1	1	3	1	1.75	0.53	0.0078
seizure duration1	50	65	87	82	47	10	62	90	61.63	9.34	
(SD1; sec)	10	4	78	5	8	8	25	16	19.25	8.73	0.0039
seizure duration2	298	240	224	210	120	10	290	191	197.88	33.41	
(SD2; sec)	10	4	215	5	8		25	16	36.38	25.63	0.0039
afterdisch.dur.1	107	77	107	82	47	10	99	89	77.25	11.83	
(ADD1; sec)	10	4	112	5	8		25	16	23.50	12.87	0.0117
afterdisch.dur.2	194	77	107	82	47	10	99	89	88.13	18.73	
(ADD2; sec)	10	4	112	5	8	8	25	16	23.50	12.87	0.0117
BODY TEMP.											<i>t-Test</i>
(°C)											
ante appl.	38.4	38.6	38.9	39.1	38.7	39.3	38.9	38.8	38.84	0.10	control
13' post appl.	38.8	38.7	38.3	38.2	37.9	38.5	38.1	38.4	38.36	0.11	0.0266
ante appl.	38.7	38.7	38.4	38.5	38.4	39.1	38.2	39.4	38.68	0.14	control
13' post appl.	37.4	38.5	38.0	38.0	37.4	38.4	38.0	37.8	37.94	0.14	0.0050

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BEHAVIOR		(score)													
		2	1	1	1	3	2	2	2	1			1.50	0.33	0.0078
antaxia	13'														
(1-6)															
abduct. hindlimb	13'														
(1-3)															
red. righting	13'	2	1			1		1		1			0.75	0.25	0.0313
(1-3)															
(flat body posture)	13'														
(1-3)															
circling	13'														
(1-3)															
Straub tail	13'														
(1-3)															
pilorection	13'														
(1-3)															
hyp locomotion	13'	2	2	1	1	2	1	1		2			1.38	0.26	0.0078
(1-3)															
hyp locomotion	13'														
(1-3)															
muscle relaxation	13'	2	2	1	1	1	2	1		2			1.38	0.26	0.0078
(1-3)															
rotarod-test	13'	+	+	+	+	+	+	+	+	+			0%		
day of exper.															

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As shown in Table 9, plasma drug levels after administration of the same dose of valproic acid and 2-propyl-4-hexynoic acid were comparable. In addition, the drug solubility test shows that the concentrations for valproic acid and 2-propyl-4-hexynoic acid are 20 mg/ml and 18.5 mg/ml respectively. Therefore, there was no marked difference in the drug concentration between the two compounds in solution, suggesting that the differences in drug potency between the two compounds were not due to differences in solubility.

Table 9

Plasma Drug Levels (in ug/ml)

	Valproic Acid	2-n-Propyl-4-Hexynoic Acid
784	173.37	154.89
785	205.44	220.70
787	174.06	180.10
788	157.83	170.68
789	190.82	225.95
791	197.82	209.31
792	189.87	201.34
793	168.89	218.87
Average	182.26	198.37

CLAIMS

1. A method of treating and/or preventing migraine and affective
5 illness in a mammal, comprising administering to said mammal a therapeutically effective amount of 2-n-propyl-4-hexynoic acid or a pharmaceutically compatible salt thereof, wherein the form of the 2-n-propyl-4-hexynoic acid is chosen from the racemate, a single enantiomer, or a non-racemic mixture of enantiomers.
- 10 2. The method of claim 1, wherein the compound is (R)-2-propyl-4-hexynoic acid.
3. The method of claim 1, wherein the compound is (S)-2-propyl-4-hexynoic acid.
- 15 4. The method of claim 1, wherein the compound is a pharmaceutically compatible salt of 2-propyl-4-hexynoic acid.
5. The method of claim 2, wherein the compound is a pharmaceutically compatible salt of (R)-2-propyl-4-hexynoic acid.
- 20 6. The method of claim 3, wherein the compound is a pharmaceutically compatible salt of (S)-2-propyl-4-hexynoic acid.
7. The method according to claim 1, wherein the 2-n-propyl-4-hexynoic acid is administered by at least one method selected from the groups consisting
25 of parentally, orally, intravenously, intramuscularly, subcutaneously and rectally.
8. The method according to claim 1, wherein the affective illness is bipolar illness.
- 30 9. The method according to claim 1, wherein the affective illness being treated is an acute phase of mania.

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10. The method according to claim 1, wherein the 2-n-propyl-4-hexynoic acid is used to prevent migraine.

5 11. The method according to claim 1, wherein the 2-n-propyl-4-hexynoic acid is administered at a dose of approximately 1 to 60 mg/kg/day.

12. The method according to claim 11, wherein the dose is at about 10-20 mg/kg/day.

10 13. The method according to claim 11, wherein the 2-n-propyl-4-hexynoic acid is used to treat mania.

14. The method according to claim 11, wherein the 2-n-propyl-4-hexynoic acid is used to treat and/or prevent migraine.

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INTERNATIONAL SEARCH REPORT

International Application No

PC/US 99/14081

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K31/19

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 94 06743 A (NAU) 31 March 1994 (1994-03-31) cited in the application page 11; example 2 page 16; example 7 page 19; example 8 & US 5 786 380 A (NAU) 28 July 1998 (1998-07-28)	1-14
A	US 5 102 913 A (HALIKAS) 7 April 1992 (1992-04-07) column 2 column 3, line 22 - line 26 column 6, line 19 - line 68 column 7, line 15 - line 21 ----- -/-	1-14



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

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Date of the actual completion of the international search

8 September 1999

Date of mailing of the international search report

21/09/1999

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Gac, G

INTERNATIONAL SEARCH REPORT

International Application No

PC 1/US 99/14081

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>ELZAMAR ET AL.: "Anticonvulsivant and neurotoxic activities of twelve analogues of valproic acid" J. PHARM. SCI., vol. 82, no. 12, December 1993 (1993-12), pages 1255-1258, XP002026656 see page 1256 table 1 compound 11</p>	1-14

INTERNATIONAL SEARCH REPORT

national application No.

PCT/US 99/14081

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 1-14
are directed to a method of treatment of the human/animal
body, the search has been carried out and based on the alleged
effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 99/14081

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9406743 A	31-03-1994	DE 4231085 A	17-03-1994
		AT 151067 T	15-04-1997
		AU 683425 B	13-11-1997
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		DE 59306054 D	07-05-1997
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